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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,088	06/15/2006	Marie-Philippe Biron	P71338US0	1568

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
01/18/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,088	BIRON, MARIE-PHILIPPE	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/15/10 and 5/21/10*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67-106* is/are pending in the application.

4a) Of the above claim(s) *72-75,81,82,87,89,92,97,99,104 and 106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-71,76-80,83-86,88,90,91,93-96,98,100-103 and 105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 15, 2010 has been entered. On May 21, 2010 Applicant submitted a Supplementary Response in which claim 95 was amended.

2. Claims 27-66 were previously pending, with claims 32-35, 41, 42, 47, 49, 52, 57, 59, 64 and 66 as containing non-elected sequences with SEQ ID NOs: 4-7 and 12-15. Applicant cancelled claims 27-66 and added new claims 67-106. Claims 72-75, 81, 82, 87, 89, 92, 97, 99, 104 and 106, which correspond to previously withdrawn claims, are withdrawn from consideration. Claims 67-71, 76-80, 83-86, 88, 90, 91, 93-96, 98, 100-103 and 105 will be examined.

3. Applicant's claim cancellations overcame all of the previously presented rejections. However, most of these rejections will be repeated for the newly added claims. Applicant's arguments regarding the previously presented rejections are addressed in the "Response to Arguments" section below.

Response to Arguments

4. Applicant's arguments filed April 15, 2010 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 67, 69, 83 and 85 under 35 U.S.C. 102(e) as anticipated by Morrissey et al., Applicant argues that Morrissey et al. do not teach DNA molecules. However, sequences of Morrissey et al. with SEQ ID NOs: 919, 931 and 1303 are DNA molecules, therefore

claims 67, 69, 83 and 85 are still anticipated. Further, the claims are drawn to oligonucleotides with certain sequences, i.e., specific structures, and oligonucleotide can have different uses, which are not altered by the intended use of the oligonucleotide.

B) Regarding the rejection of now claims 67-71, 76-80, 83-86, 88, 90, 91, 93-96 and 98 under 35 U.S.C. 103(a) as being unpatentable over Saito et al. as evidenced by Heid et al. and the GenBank sequence with accession No. X98077, Higashi et al., Stoll-Becker et al., Su et al. and Buck et al., Applicant argues the following:

i) The prior art must provide motivation which makes the claims obvious, citing several court cases. There should be both suggestion and reasonable expectation of success in the prior art. Applicant cites Ex parte Crissy and In re Warner as support for assertion that obviousness must be based on facts.

ii) "Saito teaches the quantification of the HBV DNA by quantitative RT-PCR. The Saito probe is not the "DNA" to which the present claims are limited. The probe used by Saito is complementary to a HBV DNA fragment, which is absent from in the DNA amplified with the primers as presently claimed. Saito detects the presence of the HBV DNA, the mean value of the obtained concentration of the HBV DNA being 1.8×10^3 copies/ml.

Saito does not teach primers and probes comprising SEQ ID NO. 2, 3 or 8. However, the PTO alleges that it would have been obvious to identify the sequences of alternative probes and primers, with reasonable chance of success."

iii) "Secondly, attention is directed to the fact that probes and primers according to the presently claimed invention are not alternative probes and primers to those of Saito but improved probes and primers. Indeed, Saito only studies the case of 2 patients considered as not bearing the B

or C variants of HBV. Therefore this document does not describe oligonucleotides allowing detecting all the HBV variants. To the contrary, the oligonucleotides recited in the present claims allow the detection of all the (A to G) HBV variants with the same efficiency (see table 1, page 13 and lines 1-2, page 14).

Furthermore, attention is directed to the lack of experimental data described by Saito, so the sensibility of the Saito method of detection used on a wide range of concentrations of the HBV DNA varying between 10^2 and 10^9 copies/ml cannot be validated, such as described in the present application (page 14, line 25). Indeed, the values punctually detected by Saito only vary between 250 and 2600 copies/ml (figure 1, page 328)."

iv) "Additionally, applicants find that neither Saito nor any of the cited secondary references--taken alone or in combination--teaches or suggests how to obtain probes and primers allowing an improved detection of HBV by RT-qPCR. To reject claims for obviousness under § 103 based on modifying the teachings of a reference, existence in the prior art of a reason (motivation) to effect the modification is not, by itself, sufficient to sustain the initial burden on the PTO; the "record" must show

... that it would also have been obvious how this [modification] could be achieved .... Obviousness... must not be judged by hindsight, and a "little modification" can be a most unobvious one.

In re Irani, 166 USPQ 24, 27 (CCPA 1970) (emphasis in original). Prior art relied on in a rejection under § 103 must be enabling, i.e., "if the prior art of record fails to disclose or render obvious a method of making the claimed [invention]... it may not be legally concluded that the compound was in the possession of the public. In re Hoeksema, 158 USPQ 596, 601 (CCPA 1968)."

v) "Therefore, none of the above documents teaches nor suggests how to obtain primers and probes allowing detecting HBV on a wide range of concentrations of DNA, with an improved sensibility with regard to Saito and in addition allowing to detect all HBV variants."

vi) Buck et al. reference is not applicable to the instant case because

"- The test sequence used by Buck is an "ideal" synthetic sequence, which contains no region susceptible to affect elongation, and not a region of the HBV genome susceptible to contain repetitions or secondary structures which can render more difficult hybridization of the primers and elongation.

- The participants of the survey were free to place their primers wherever they wished in the proposed test sequence. Buck note, that apparently, certain segments of the sequence were voluntarily excluded by the participants. On the contrary, in the case of detection of HBV, the choice of the segment to be amplified is essential to allow the detection of all the genotypes of the HBV and fragment cannot be chosen.

- The participants of the survey had to design only 5' primers to be used only for a sequencing, which an amplification by PCR requires a couple of primers with compatible physical and chemical characteristics. Generally speaking, the choice of a couple of primers is subjected to requirements concerning their length, their Tm, their percentage in G-C, the absence of repetitions and secondary structures, the presences of G-C nucleotides in 3', the low chance that these primers form dimers of primers and the compatibility of both primers of the stone couple (in particular, same Tm, the same conditions of PCR).

- So, the conclusions of Buck allow by no means concluding that it is obvious to obtain probes and primers allowing detecting HBV by RT-qPCR. Buck does not allow concluding that it is obvious to obtain probes and primers allowing HBV with an improved sensibility, either. Moreover, Buck does not allow concluding that it is obvious to obtain probes and primers suitable for detecting all HBV variants."

Before answering Applicant's arguments, let us start from the facts on which the rejection is based. The positions of primers and probes for all of the references were mapped to a single HBV genome sequence, with GenBank Accession No. X98077, to facilitate discussion. The following table summarizes the positions of primers, probes and amplicons produced using either Applicant's oligonucleotides or oligonucleotides used in the prior art:

Reference	Primer-forward	Primer-reverse	Probe	Amplicon
Instant claims	1440-1457	1582-1602	1527-1548	1440-1602
Saito et al.	1414-1435	1728-1744	1681-1705	1414-1744
Higashi et al.	1433-1455	1588-1610		1433-1610
Su et al.	1561-1580	1755-1774		1561-1774
Stoll-Becker et al.	1380-1401	1529-1550		1380-1550

The following conclusions are based on the results of amplification with the above primers used in the prior art:

a) The region of the X gene between bp 1380 to 1774 can be successfully amplified using different combinations of primers.

b) The region amplified by instantly claimed primers lies entirely within the region successfully amplified by Saito et al. and overlaps between bp 1440-1550 with the region amplified by primers of Stoll-Becker et al.

c) The region amplified by instant primers is entirely encompassed by the region amplified by Higashi et al., and only 15 bp shorter than amplicon generated by the primers of Higashi et al. Further, the forward primer of Higashi et al. overlaps with the instant primer over bp 1440-1455, i.e., 16 of the 18 bp, and the reverse primer of Higashi et al. overlaps with the instant primer over bp 1588-1602, i.e., 15 of the 21 bp.

Therefore, regarding i), iv) and v), the obviousness rejection is based on factual state of the art at the time of the invention, when the sequences of hundreds of HBV isolates were known, as were the techniques for selecting primers and probes for DNA amplification, both by PCR and its variants, such as real-time PCR and quantitative real-time PCR. Applicant is directed to the review of Mackay et al. (Nucl. Acids Res., vol. 30, pp. 1292-1305, 2002), describing in detail applications of real-time PCR specifically in virology, detailing the different techniques, including quantitative real-time PCR, and 209 references detailing amplification of different viruses by PCR, real-time PCR and quantitative real-time PCR. In conclusion, the rejection is based on the enabling disclosure of the references cited in the rejection and the state of the art at the time of the invention was filed.

Regarding motivation and suggestion, it is very clearly articulated by the Supreme Court in KSR v. Teleflex (82 USPQ 2d 1385, 2007), that in case where there is a limited number of possibilities, "obvious to try" is obvious, and that the rigid test of TSM is not always applicable:

"Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. Helpful insights,

however, need not become rigid and mandatory formulas. If it is so applied, the TSM test is incompatible with this Court's precedents. The diversity of inventive pursuits and of modern technology counsels against confining the obviousness analysis by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasizing the importance of published articles and the explicit content of issued patents. In many fields there may be little discussion of obvious techniques or combinations, and market demand, rather than scientific literature, may often drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, for patents combining previously known elements, deprive prior inventions of their value or utility. Since the TSM test was devised, the Federal Circuit doubtless has applied it in accord with these principles in many cases. There is no necessary inconsistency between the test and the Graham analysis. But a court errs where, as here, it transforms general principle into a rigid rule limiting the obviousness inquiry."

In re Kubin (90 USPQ2d 1417, 2009) presents a detailed analysis of the applicability of "obvious to try" reasoning applied to the 103 rejections:

"…..The Supreme Court repudiated as “error” the Deuel restriction on the ability of a skilled artisan to combine elements within the scope of the prior art:

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was “obvious to try.” When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

KSR, 550 U.S. at 421 (internal citation omitted) (emphasis added).

The Supreme Court's admonition against a formalistic approach to obviousness in this context actually resurrects this court's own wisdom in In re O'Farrell, which predates the Deuel decision by

some seven years. This court in O'Farrell cautioned that "obvious to try" is an incantation whose meaning is often misunderstood:

> It is true that this court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under §103. However, the meaning of this maxim is sometimes lost. Any invention that would in fact have been obvious under §103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?

In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988). To differentiate between proper and improper applications of "obvious to try," this court outlined two classes of situations where "obvious to try" is erroneously equated with obviousness under §103. In the first class of cases,

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

Id. In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness. The inverse of this proposition is succinctly encapsulated by the Supreme Court's statement in KSR that where a skilled artisan merely pursues "known options" from a "finite number of identified, predictable solutions," obviousness under §103 arises. 550 U.S. at 421.

The second class of O'Farrell's impermissible "obvious to try" situations occurs where

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

853 F.2d at 903. Again, KSR affirmed the logical inverse of this statement by stating that §103 bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions." 550 U.S. at 417.

This court in O'Farrell found the patentee's claims obvious because the Board's rejection of the patentee's claims had not presented either of the two common "obvious to try" pitfalls. Specifically,

this court observed that an obviousness finding was appropriate where the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful." 853 F.2d at 902 (emphasis added). Responding to concerns about uncertainty in the prior art influencing the purported success of the claimed combination, this court stated: "[o]bviousness does not require absolute predictability of success … all that is required is a reasonable expectation of success." Id. at 903-04 (emphasis added). The Supreme Court in KSR reinvigorated this perceptive analysis."

Therefore, looking at the criteria which might not make "obvious to try" obvious, it is clear that neither one applies. The PCR amplification has been practiced all over the world for over 30 years now, and real-time PCR has been around for over 20 years, and has been successfully applied to amplification of target nucleic acids from different organisms, including viruses. Further, a number of references have amplified the same region of HBV genome successfully. Therefore, one of ordinary skill in the art would be presented with well-known amplification methodology and a limited number of possibilities for selection of primers, since the cited references clearly outline a region which is successfully amplified.

Regarding ii) and iii), Applicant argues limitations which are not in the claims. Further, if Applicant's primers amplify all HBV types, so would the primers of Higashi et al., for example. As to the sensitivity of detection, there are no claim limitations requiring a particular detection sensitivity.

Regarding vi), Buck et al. is very much relevant to the instant case. The HBV sequences to be amplified were known in the art and successfully amplified, therefore one would have a reasonable expectation of success choosing a primer pair anywhere within the region amplified by Saito et al. Further, primer selection, as correctly pointed out by Applicant, requires consideration

of several factors, such as melting temperature and amplification conditions. However, in view of the fact that PCR has been practiced for over 30 years, primer selection has become a routine procedure, aided by a multitude of primer selection programs. Routine experimentation is not considered to be inventive, as noted in In re Aller, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

For the reasons presented above the rejections of newly-submitted claims are made over the same combination of references as presented previously.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 67, 69, 83 and 85 are rejected under 35 U.S.C. 102(e) as being anticipated by Morrissey et al. (US 2003/0206887 A1; filed September 16, 2002).

Regarding claims 67 and 69, Morrissey et al. teach DNA sequences comprising SEQ ID NO: 2 and 3 (see sequence search results below) (SEQ ID NO: 919, 931 and 1303; Table II).

```
US-10-244-647-919/c
; Sequence 919, Application US/10244647
; Publication No. US20030206887A1
; GENERAL INFORMATION:
;  APPLICANT: Ribozyme Pharmaceutical, Inc.
;  APPLICANT:  Morrissey, David
;  APPLICANT:  McSwiggen, James
;  APPLICANT:  Beigelman, Leonid
```

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;  TITLE OF INVENTION: RNA Interference Mediated Inhibition of Hepatitis B Virus
(HBV) Using
;  TITLE OF INVENTION:  Short Interfering Nucleic Acid (siNA)
;  FILE REFERENCE: 400/060 (MBHB02-1000)
;  CURRENT APPLICATION NUMBER: US/10/244,647
;  CURRENT FILING DATE:  2003-04-14
;  PRIOR APPLICATION NUMBER: US 60/358,580
;  PRIOR FILING DATE: 2002-02-20
;  PRIOR APPLICATION NUMBER: US 60/393,924
;  PRIOR FILING DATE: 2002-07-03
;  PRIOR APPLICATION NUMBER: PCT US02/09187
;  PRIOR FILING DATE: 2002-03-26
;  PRIOR APPLICATION NUMBER: US 60/296,876
;  PRIOR FILING DATE: 2001-06-08
;  NUMBER OF SEQ ID NOS: 1524
;  SOFTWARE: PatentIn version 3.0
; SEQ ID NO 919
;   LENGTH: 19
;   TYPE: RNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Description of Artificial Sequence:  siNA antisense
region
US-10-244-647-919

  Query Match             100.0%;  Score 18;  DB 8;  Length 19;
  Best Local Similarity   100.0%;  Pred. No. 80;
  Matches   18;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GCTGAATCCCGCGGACGA 18
              ||||||||||||||||||
Db         19 GCTGAATCCCGCGGACGA 2



RESULT 5
US-10-244-647-931/c
; Sequence 931, Application US/10244647
; Publication No. US20030206887A1
; GENERAL INFORMATION:
;  APPLICANT: Ribozyme Pharmaceutical, Inc.
;  APPLICANT:  Morrissey, David
;  APPLICANT:  McSwiggen, James
;  APPLICANT:  Beigelman, Leonid
;  TITLE OF INVENTION: RNA Interference Mediated Inhibition of Hepatitis B Virus
(HBV) Using
;  TITLE OF INVENTION:  Short Interfering Nucleic Acid (siNA)
;  FILE REFERENCE: 400/060 (MBHB02-1000)
;  CURRENT APPLICATION NUMBER: US/10/244,647
;  CURRENT FILING DATE:  2003-04-14
;  PRIOR APPLICATION NUMBER: US 60/358,580
;  PRIOR FILING DATE: 2002-02-20
;  PRIOR APPLICATION NUMBER: US 60/393,924
;  PRIOR FILING DATE: 2002-07-03
;  PRIOR APPLICATION NUMBER: PCT US02/09187
;  PRIOR FILING DATE: 2002-03-26
```

```
;  PRIOR APPLICATION NUMBER: US 60/296,876
;  PRIOR FILING DATE: 2001-06-08
;  NUMBER OF SEQ ID NOS: 1524
;  SOFTWARE: PatentIn version 3.0
; SEQ ID NO 931
;   LENGTH: 19
;   TYPE: RNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Description of Artificial Sequence:  siNA antisense
region
US-10-244-647-931

  Query Match             100.0%;  Score 18;  DB 8;  Length 19;
  Best Local Similarity   100.0%;  Pred. No. 80;
  Matches   18;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GCTGAATCCCGCGGACGA 18
              ||||||||||||||||||
Db         18 GCTGAATCCCGCGGACGA 1


RESULT 3
US-10-244-647-1303/c
; Sequence 1303, Application US/10244647
; Publication No. US20030206887A1
; GENERAL INFORMATION:
;  APPLICANT: Ribozyme Pharmaceutical, Inc.
;  APPLICANT:  Morrissey, David
;  APPLICANT:  McSwiggen, James
;  APPLICANT:  Beigelman, Leonid
;  TITLE OF INVENTION: RNA Interference Mediated Inhibition of Hepatitis B Virus
(HBV) Using
;  TITLE OF INVENTION:  Short Interfering Nucleic Acid (siNA)
;  FILE REFERENCE: 400/060 (MBHB02-1000)
;  CURRENT APPLICATION NUMBER: US/10/244,647
;  CURRENT FILING DATE:  2003-04-14
;  PRIOR APPLICATION NUMBER: US 60/358,580
;  PRIOR FILING DATE: 2002-02-20
;  PRIOR APPLICATION NUMBER: US 60/393,924
;  PRIOR FILING DATE: 2002-07-03
;  PRIOR APPLICATION NUMBER: PCT US02/09187
;  PRIOR FILING DATE: 2002-03-26
;  PRIOR APPLICATION NUMBER: US 60/296,876
;  PRIOR FILING DATE: 2001-06-08
;  NUMBER OF SEQ ID NOS: 1524
;  SOFTWARE: PatentIn version 3.0
; SEQ ID NO 1303
;   LENGTH: 23
;   TYPE: RNA
;   ORGANISM: Hepatitis B virus
US-10-244-647-1303

  Query Match             100.0%;  Score 21;  DB 8;  Length 23;
  Best Local Similarity   100.0%;  Pred. No. 14;
```

```
  Matches   21;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy           1 GTGCAGAGGTGAAGCGAAGTG 21
               |||||||||||||||||||||
Db          21 GTGCAGAGGTGAAGCGAAGTG 1
```

Regarding claims 83 and 85, Morrissey et al. teach using multiple siRNA sequences in the silencing reactions, which involves hybridization of the oligonucleotides with HBV mRNA (page 6, [0048]; page 14, [0111]).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 67-71, 76-80, 83-86, 88, 90, 91, 93-96 and 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saito et al. (J. Med. Virol., vol. 58, pp. 325-331, 1999; cited in the previous office action) as evidenced by Heid et al. (Genome Res., vol. 6, pp. 986-994, 1996; cited in the previous office action) and the GenBank sequence with accession No. X98077 (1997; cited in the previous office action), Higashi et al. (Liver, vol. 22, pp. 374-379, October 2002; cited in the previous office action), Stoll-Becker et al. (J. Virol., vol. 71, pp. 5399-5407, 1997; cited in the previous office action), Su et al. (Clin. Cancer Res., vol. 7, pp. 2005-2015, 2001; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action).

A) As a reference for further discussion, the positions of claimed SEQ ID NO: 2, 3 and 8 with respect to the HBV genome with GenBank accession No. are as follows (see BLAST

alignment): SEQ ID NO: 2; bp 1440-1457; SEQ ID NO: 3: bp 1582-1602; SEQ ID NO: 8: bp 1527-1548.

Regarding claims 67-71, 77-80, 83-86, 88, 90 and 91, Saito et al. teach a set of three DNA oligonucleotides, each between 15 and 40 bp long, for the detection of the X gene of HBV (page 326, last paragraph). The position of these primers and probe are as follows with respect to the HBV wild-type genome sequence with GenBank accession No. X98077 (see BLAST alignment of these sequences): the first primer hybridizes between bp 1414-1435 of that sequence, the second primer with bp 1728-1744, and the probe with bp 1681-1705. Therefore, the amplicon produced by Saito et al. overlaps with the amplicon produced by the instant primers between bp 1440-1602, i.e., the amplicon produced using the instant primers is 100% contained within the amplicon produced by the primers of Saito et al.

Regarding claim 80, Saito et al. teach the probes were TaqMan probes according to Heid et al. (page 325, second paragraph). As evidenced by Heid et al., TaqMan probes comprise a fluorophore and a quencher (page 987, second and third paragraph), anticipating the limitations of an oligonucleotide comprising a fluorophore and a quencher.

Regarding claim 76, Saito et al. teach the use of oligonucleotides to detect HBV (page 326, last paragraph; page 327, first paragraph); since the primers hybridize to the HBV, the method of claim 36 is anticipated.

Regarding claim 93, Saito et al. teach a method comprising:

a) contacting a set of oligonucleotides according to claim 43 with a biological sample or nucleic acid preparation obtained from a biological sample, under conditions suitable for the oligonucleotides to hybridize to a HBV nucleic acid present in the sample (page 326, last paragraph; page 327, first paragraph);

b) amplifying said HBV nucleic acid using said oligonucleotides as primers (page 326, last paragraph; page 327, first paragraph);

c) detecting the amplification product, indicative of the presence of a HBV in the biological sample (page 326, last paragraph; page 327, first paragraph).

Regarding claim 94, Saito et al. teach PCR (page 326, last paragraph).

Regarding claims 95, 96 and 98, Saito et al. teach a probe for the X gene of HBV virus (page 326, last paragraph), which hybridizes to the bp 1681-1705 of the GenBank accession No. X98077. Saito et al. teach that the probes were TaqMan probes according to Heid et al. (page 325, second paragraph). As evidenced by Heid et al., TaqMan probes comprise a fluorophore and a quencher (page 987, second and third paragraph), anticipating the limitations of an oligonucleotide comprising a fluorophore and a quencher.

B) Saito et al. do not specifically teach primers and probes 15-40 bp in length comprising or consisting of SEQ ID NO: 2, 3 or 8.

However, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used the known sequences of the HBV genome to design primers and probes for the detection of the genome with a high expectation of success. In In Re Deuel 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because

homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of HBV virus, and in particular for the detection of the X protein, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are prima facie obvious over the cited references in the absence of secondary considerations.

The expectation of success of using alternative primers derived from the sequence is provided by the references listed below.

Higashi et al. amplified HBV virus X protein by PCR using two sets of primers (page 375, paragraphs 5-9). These primers hybridize to the following regions of the X98077 sequence (see BLAST alignment): OAL-X1: bp 1433-1455, OAL-X4: bp 1588-1610. These primers create an amplicon which is shifted 5' with respect to the instant amplicon by 7 bp.

Stoll-Becker et al. teach detection of HBV X gene by PCR using primers P1 and P2 (page 5400, sixth paragraph; Table 1), which hybridize to the following regions of the X98077 sequence (see BLAST alignment): P1: bp 1380-1401, P2: bp 1529-1550. Therefore the amplicon generated by the primers of Stoll-Becker et al. overlaps with the amplicon generated by the instant primers between bp 1440-1550.

Finally, Su et al. teach amplification of the HBV virus in circulation of infected patients by PCR using primers directed to the X gene (page 2006, paragraphs 5 and 6), txs3 and xas1. As can be seen from the alignment of the txs3 primer with the GenBank sequence X98077, the txs3 primer

hybridizes to a region between bp 1561-1580, i.e., within the amplicon generated by the instant primers.

As can be seen from the above references, selection of primers from the different and overlapping regions of the X gene produced successful amplification of the HVB sequences.

Buck et al. expressly provides evidence of the equivalence of primers in support of the above conclusion regarding primer selection from a known sequence. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

9. Claims 100-103 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saito et al. (J. Med. Virol., vol. 58, pp. 325-331, 1999; cited in the previous office action) as evidenced by Heid et al. (Genome Res., vol. 6, pp. 986-994, 1996; cited in the previous office

action) and the GenBank sequence with accession No. X98077 (1997; cited in the previous office action), Higashi et al. (Liver, vol. 22, pp. 374-379, October 2002; cited in the previous office action), Stoll-Becker et al. (J. Virol., vol. 71, pp. 5399-5407, 1997; cited in the previous office action), Su et al. (Clin. Cancer Res., vol. 7, pp. 2005-2015, 2001; cited in the previous office action), Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action), Pasupuletti et al. (U.S. Patent No. 6,635,428 B2; cited in the previous office action) and Stratagene Catalog (p. 39, 1988; cited in the previous office action).

Regarding claims 100, 101, 103 and 105, Saito et al. teach a set of three oligonucleotides, two primers and a probe, each between 15 and 40 bp long, for the detection of the X gene of HBV (page 326, last paragraph). The position of these primers and probe are as follows with respect to the HBV wild-type genome sequence with GenBank accession No. X98077 (see BLAST alignment of these sequences): the first primer hybridizes between bp 1414-1435 of that sequence, the second primer with bp 1728-1744, and the probe with bp 1681-1705. Therefore, the amplicon produced by Saito et al. overlaps with the amplicon produced by the instant primers between bp 1440-1602, i.e., the amplicon produced using the instant primers is 100% contained within the amplicon produced by the primers of Saito et al.

Regarding claims 103 and 105, Saito et al. teach the probes were TaqMan probes according to Heid et al. (page 325, second paragraph). As evidenced by Heid et al., TaqMan probes comprise a fluorophore and a quencher (page 987, second and third paragraph), anticipating the limitations of an oligonucleotide being detectably labeled.

Regarding claim 102, Saito et al. teach PCR (page 326, last paragraph).

B) Saito et al. do not specifically teach primers and probes 15-40 bp in length comprising or consisting of SEQ ID NO: 2, 3 or 8.

However, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used the known sequences of the HBV genome to design primers and probes for the detection of the genome with a high expectation of success. In In Re Deuel 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

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Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of HBV virus, and in particular for the detection of the X protein, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are prima facie obvious over the cited references in the absence of secondary considerations.

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As can be seen from the above references, selection of primers from the different and overlapping regions of the X gene produced successful amplification of the HVB sequences.

Buck et al. expressly provides evidence of the equivalence of primers in support of the above conclusion regarding primer selection from a known sequence. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535,

column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

C) None of the above references teaches kits.

D) Regarding claims 100-103 and 105 Pasupuletti et al. teach kits for the PCR detection of HBV in real-time (col. 5, lines 64-67; col. 6, lines 1-9).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to package the primers and probes for the detection of HBV by the methods of Saito et al., Higashi et al., Stoll-Becker et al., Su et al. and Buck et al. as suggested by Pasupuletti et al. Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

10. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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